UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,173	06/24/2004	Katsuhito Takahashi	4439-4022	3299

27123 7590 10/29/2009

MORGAN & FINNEGAN Transition Team
C/O Locke Lord Bissell & Liddell
3 WORLD FINANCIAL CENTER
NEW YORK, NY 10281-2101

EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
10/29/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Shopkins@Lockelord.com
OWalker@Lockelord.com

Office Action Summary	Application No.	Applicant(s)	
	10/500,173	TAKAHASHI ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,7,20,21,25,26,35 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,7,20,21,25,26,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/12/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/10/2009 has been entered.

Claims 2-5, 8-19, 22-24 and 27-34 have been cancelled. Claims 1, 6, 20, 21, 25 and 35 have been amended.

Claims 1, 6, 7, 20, 21, 25, 26, 35, and 36 are pending and under examination.

2. All rejections pertaining to claims 23 and 24 are moot because Applicant cancelled the claims in the reply filed on 08/10/2009.

Specification

3. The substitute specification submitted by Applicant on 08/10/2009 is objected to because it is replete with terms which are not clear, concise and exact. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or verbose terms used in the specification are: p. 9 (first full paragraph reciting: "vector, which can specifically suppress the expression and replication at a desired period"; while the specification and

the claims contemplate a vector capable of suppressing its expression and replication, such is not clearly stated); p. 9 ("obtaining a transcriptional initiation regulatory region in the cells of a human calponin gene"); p. 10 ("specificity against acyclovir" or "a virus mixed solution was infected after homologous recombination into a Vero E5 cell and ICP4 cDNA was introduced"); p. 13 (paragraph describing Fig. 4); p. 26 (first full paragraph).

Furthermore, the substitute specification is replete with grammatical errors and typos. Examples of some grammatical errors and typos are: "which was used to used to infect" (p. 6); inframe (p. 20); "a human calponin gene that specifically express in specific tumor cells' (p. 9); "albumin prompter" (p. 10, first full paragraph); "once homologous recombination is successfully occurred (p. 11, second full paragraph); "transfected cells was cultured" (p. 31, first full paragraph).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 6, 7, 20, 21, 25, 35, and 36 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. (U.S. Patent No. 5,728,379, of record), in view of each Yamamura et al. (Cancer Res 5/2001, 61: 3969-3977, of record), Wagstaff et al.

(Gene Therapy, 1998, 5: 1566-1570, of record) and Foster et al. (J. Virol. Methods, 1998, 75: 151-160, of record).

Martuza et al. teach expressing therapeutic factors into tumor cells *in vivo* by introducing into the cells an HSV vector comprising a DNA fragment comprising a tissue-specific promoter, the ICP4 gene downstream to the tissue-specific promoter, *lacZ* upstream to the tissue-specific promoter, and tissue-specific enhancers upstream to the tissue-specific promoters, wherein the tissue specific promoter is derived from genes highly expressed in tumor cells (i.e., the vector replicates and expresses the therapeutic factors in proliferating cells which express the gene driven by the tissue-specific promoter; the vector does not replicate in adult normal cells). The vector is obtained by inserting the DNA fragment into a locus other than the HSV *tk* locus by homologous recombination. Since it has an intact thymidine kinase, the vector is sensitive to ganciclovir and its replication can be suppressed at the desired time by treatment with ganciclovir (claims 1, 6, 20, 21 and 25) (column 4, lines 37-59; Figure 1 and its Brief description at column 6, lines 42-45; column 7, lines 20-35; column 10, lines 30-67; column 11, lines 4-16; column 25, lines 39-56; column 33, lines 48-64; claims 1-3, 12, and 13). Martuza et al. teach inserting their DNA fragment into the ribonucleotide reductase gene locus by homologous recombination; homologous recombination takes place by co-transfecting the DNA fragment with an HSV vector lacking a functional ICP4 and comprising an endogenous thymidine kinase into Vero cells (i.e., cells which do not express ICP4 and which contain transcription factors that activate the calponin promoter, see Example A of the instant specification), screening

and purifying clones based on the expression of the *lacZ*-encoded β-galactosidase (claims 1, 35, and 36) (Fig. 4 and 5, column 5, lines 1-9 and 39-45, column 21, lines 40-60, Example 1). Martuza et al. teach that ribonucleotide reductase gene disruption is essential for therapeutic vectors, wherein disruption results in increased sensitivity to acyclovir and ganciclovir and wherein the ribonucleotide reductase-disrupted vectors are less likely to replicate in normal cells (column 22, lines 1-3 and 24-40, column 25, lines 57-62). With respect to the limitation of cloning without agarose overlay (claim 35), the instant end product (i.e., the HSV vector) is identical to the end product taught by the combined teachings above, regardless of whether cloning takes place with or without agarose overlay. Applicant did not provide any evidence that cloning in the absence of agarose overlay results in an HSV vector which is structurally different from the HSV vector taught by the cited prior art.

Although Martuza et al. teach a cell-specific promoter and an enhancer, they do not specifically teach the full length calponin promoter or the 4F2 enhancer (claims 1 and 7). Yamamura et al. teach the calponin promoter (i.e., a promoter region comprising SEQ ID NO: 3) driving the expression of the ICP4 gene and the 4F2 enhancer, wherein the 4F2 enhancer is integrated upstream to the calponin promoter and wherein the 4F2 enhancer further upregulates ICP4 expression (p. 3970, column 1, fourth full paragraph and Figure 1A and 1B, p. 3972, column 1, first paragraph). Yamamura et al. also teach that calponin is highly expressed in a variety of human soft tissue and bone tumors (Abstract, p. 3969, column 2, p. 3976, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the

HSV vector of Martuza et al. by using the calponin promoter together with the 4F2 enhancer, with a reasonable expectation of success. One of skill in the art would have been motivated to use the calponin promoter in order to target therapeutics to the human soft and bone tumor cells. One of skill in the art would have been motivated to use the 4F2 enhancer because Yamamura et al. teach that insertion of the 4F2 enhancer upstream of the calponin promoter increases the transcriptional activity of the calponin promoter (p. 3972, column 1). One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a vector because the art teaches that such vectors can be successfully made and because Martuza et al. teach that promoters derived from genes highly expressed in tumor cells can be successfully used to specifically drive vector replication in tumor cells.

Martuza et al. and Yamamura et al. do not teach inserting the EGFP gene downstream to the ICP4 gene via IRES (claims 1 and 35). However, at the time the invention was made, the use of IRES to obtain bicistronic HSV vectors expressing GFP as a reporter to identify the transduced cells was taught by the prior art (see Wagstaff et al., Abstract, p. 1567, Fig. 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the vector of Martuza et al. and Yamamura et al. by inserting GFP downstream to ICP4 via IRES to achieve the predictable result of identifying the transduced cells. While Wagstaff et al. teach GFP and not EGFP, it is noted that EGFP was known and used in the prior art (see Foster et al., Abstract).

Therefore, one of skill in the art would have known to substitute GFP with EGFP to achieve the predictable result of identifying transduced cells.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant's arguments are answered below to the extent that they pertain to the instant rejection.

Applicant argues that, although the Examiner indicates that "Martuza et al. teach that ribonucleotide reductase gene disruption is essential for therapeutic vectors, wherein the ribonucleotide reductase- disrupted vectors are less likely to replicate in normal cells, such description only pertains to TK^- vectors, and the reason for this is shown as follows: "Because TK^- HSV-1 mutants known in the art are resistant to these anti-viral agents, such mutants could be difficult to eliminate in the event of systemic infection or encephalitis." (column 22, lines 27-29). Applicant argues that, since Martuza teaches that RR disruption is essential only for TK^- vectors and suggests nothing about the importance of RR disruption in TK^+ vectors, the teaching of Martuza would not motivate one skilled in the art to select ribonucleotide reductase gene as a region for the insertion of a DNA fragment when using a TK^+ vector. Applicant points out that claims 1 and 35 presently recite that the HSV vector comprises an endogenous thymidine kinase gene. Therefore, the instant invention would not have been obvious based at least on the teachings of Martuza et al.

Applicant argues that, when the DNA fragment of Martuza is introduced into the ribonucleotide reductase locus while the *tk* gene is left intact, it is impossible to select recombinants based on the sensitivity to ganciclovir. Selection of recombinants based on the sensitivity to ganciclovir is only enabled when the DNA fragment is inserted into the *tk* locus.

Applicant argues that Martuza's group was only able to produce the HSV vector comprising the ICP4 gene which is linked to a cell-specific promoter inserted in the ribonucleotide reductase locus for the first time in 2006, well after the date of Martuza and Chung provided the alleged teachings to produce the vector of the instant invention.

In response to Applicant's previous arguments, the Examiner contends that "making a construct [of the instant invention] was routine in the prior art, as demonstrated by Chung." (Office Action; pg. 12; lns. 9-12). Applicant argues that the construct of Chung was produced by the steps of transfecting Vero cells with a linearized gene fragment and the vector, harvesting virus progeny when cytopathic effect by the γ34.5 gene expression were evident, and confirming deletion of the *lacZ* gene by Southern blot analysis and agarose overlay assay, thus isolating the recombinant vector of the interest, as described in page 7557, column 1. However, a screening method using cytopathic effect and agarose overlay assay as that of Chung cannot be applied to production (selecting) of the vector of the present invention. Therefore, making a construct of the instant invention can not be considered routine as suggested by the Examiner.

With respect to the teaching of the calponin promoter and the 4F2 enhancer of the instant invention, the Examiner acknowledges that Martuza does not teach the full length calponin promoter or the 4F2 enhancer, but they are allegedly taught by Yamamura. Specifically, Yamamura teaches a calponin promoter which promotes expression of the ICP4 gene, and the 4F2 enhancer which is integrated to the upstream of the calponin promoter and which enhances expression of ICP4. However, Applicant argues that it is extremely difficult to produce a recombinant where the Yamamura's sequence consisting of the 4F2 enhancer, calponin promoter, and ICP4 is introduced into a region other than the TK locus in the HSV vector. It became possible to produce the vector of the instant invention at last by adding another marker sequence (adding EGFP to the downstream of IRES) to the introductory sequence of Yamamura et al. so as to enabling a reliable screening of recombinants to a region other than the TK locus in the HSV vector. While Wagstaff show that the use of an IRES enables the translation of two reporter genes from a single mRNA transcript derived by a single promoter (Abstract, right column, lines 3-8), in the instant invention, two marker genes are controlled by different promoters. *lacZ* is placed upstream to the calponin promoter and EGFP is placed downstream to the ICP4, which is under the control of the calponin promoter. Essentially, the two markers are translated from different mRNAs, not from the same mRNA taught by Wagstaff. Hence, the HSV vector prepared following the teachings of Martuza, Yamamura, and Wagstaff would not function/operate with its intended purpose and, therefore, can not be used as the basis for the *prima facie* obviousness rejection.

Applicant asserts that, since none of the references either alone or in combination discloses all of the elements to produce the claimed HSV vector, the rejection should be withdrawn.

Applicant's arguments are acknowledged; however, they are not found persuasive for the following reasons:

Applicant argues that Martuza teaches that RR disruption is essential only for TK^- vectors and suggests nothing about the importance of RR disruption in TK^+ vectors. This is incorrect. The full citation on column 22, lines 27-29 is:

> An important difference between ribonucleotide reductase deficient (RR^-) and other herpes simplex virus mutants is hrR3's hypersensitivity to acyclovir and gancyclovir. Because TK^- HSV-1 mutants known in the art are resistant to these anti-viral agents, such mutants could be difficult to eliminate in the event of systemic infection or encephalitis."

Therefore, the hrR3' HSV vector of Martuza et al. (which is RR^-) must necessarily be TK^+, otherwise it would not be hypersensitive to acyclovir and gancyclovir (see also column 3, lines 25-28, column 21, lines 53-55 and column 25, lines 21-24 in Martuza et al.). Even the instant specification teaches that the hrR3' HSV vector is hypersensitive to gancyclovir (see the instant specification, p. 13, third full paragraph). Furthermore, Martuza et al. also teach the $RR^- TK^+$ G207 HSV vector which is sensitive to gancyclovir (column 29, lines 9-67; column 33, lines 49-64; Fig 4 and 5). Clearly, Martuza et al. teach $RR^- TK^+$ HSV vectors.

Applicant argues that, when the DNA fragment of Martuza is introduced into the ribonucleotide reductase locus while the *tk* gene is left intact, it is impossible to select

recombinants based on the sensitivity to ganciclovir. First, it is noted that, by making this argument, Applicant admits that Martuza et al. teach vectors with an intact *tk* gene. Second, the fact that such vectors cannot be selected based on their sensitivity to ganciclovir is irrelevant to the instant claims and rejection which do not require ganciclovir selection.

Applicant argues that a screening method using cytopathic effect and agarose overlay assay as that of Chung cannot be applied to production (selecting) of the vector of the present invention. This is just an argument not supported by any evidence, and therefore not found persuasive. RR^-TK^+ HSV vectors such as the instant vectors can be selected using cytopathic assay and agarose overlay assays (see Martuza et al., column 29, lines 1-59). Moreover, the rejection is not based on Chung et al. (Chung was previously cited in response to Applicant's argument that one of skill in the art would not have had a reasonable expectation of success in introducing foreign genes into the ribonucleotide reductase locus; similar to Martuza et al., Chung et al. provide evidence that homologous recombination into the ribonucleotide reductase locus was routine in the prior art). The rejection is based on a combination of references teaching a vector comprising *lacZ* and EGFP, which *lacZ* and EGFP can be used to select for recombinants.

Applicant argues that it is extremely difficult to introduce Yamamura's sequence consisting of the 4F2 enhancer, calponin promoter, and ICP4 into a region other than the TK locus in the HSV vector. This argument is not found persuasive because it is not supported by any evidence.

Applicant argues that it became possible to produce the vector of the instant invention at last by adding another marker sequence (adding EGFP to the downstream of IRES) to the introductory sequence of Yamamura et al. so as to enabling a reliable screening of recombinants to a region other than the TK locus in the HSV vector. This argument is not found persuasive because Martuza et al. do teach obtaining RR^-TK^+ HSV vectors (i.e., they provide a reliable screening of recombinants to a region other than the TK locus in the HSV vector).

Applicant argues that, as opposed to Wagstaff, in the instant invention, the two marker genes are controlled by different promoters and are therefore translated from different mRNAs. In response to this argument, it is noted that IRES operably couples two different mRNAs to the same promoter. Therefore, EGFP and LacZ of Wagstaff et al. are translated from different mRNAs and not from the same mRNA, as Applicant argues. Moreover, the rejection states that the EGFP is inserted downstream to ICP4. It would have been within the capabilities of one of skill in the art to insert IRES-EGFP downstream of ICP4 such that the EGFP is expressed from the calponin promoter. Therefore, the vector taught by the combination of references cited above does function according to its intended purpose.

For the reasons set forth above, the rejection is maintained.

6. Claims 1, 6, 7, 20, 21, 25, 26, 35, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. taken with each Yamamura et al., Wagstaff et al., and Foster et al., in further view of Miyatake et al. (Stroke, 1999, 30: 2431-2439).

The teachings of Martuza et al., Yamamura et al., Wagstaff et al., and Foster et al. are applied as above for claims 1, 6, 7, 20, 21, 25, 35, and 36. Martuza et al., Yamamura et al., Wagstaff et al., and Foster et al. do not teach therapy by targeting the virus to proliferating smooth muscle cells (claim 26). However, at the time the invention was made, therapy by specific targeting proliferating smooth muscle cells was taught by the prior art. For example, the prior art teaches using tissue specific replication competent HSV vectors to inhibit smooth muscle cell proliferation (see Miyatake et al., the whole paper). One of skill in the art would have known, would have been motivated, and would have been expected to have a reasonable expectation of success in using the vector taught by Martuza et al., Yamamura et al., Wagstaff et al., and Foster et al. (i.e., replication competent and, since calponin is highly expressed in proliferating smooth muscle cells, specific for proliferating smooth muscle cells) to treat disorders associated with smooth muscle cell proliferation. One of skill in the art would have expected to have a reasonable expectation of success in doing such because the art teaches that replication competent HSV can be successfully used to treat disorders associated with cell proliferation, including those characterized by smooth muscle proliferation.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant traversed the instant rejection on the grounds that the results would not be predictable without undue experimentation because Miyatake teaches a self-

replicable HSV vector that is not cell-specific and substantially different from the cell-specific vector of the instant invention as discussed above. In particular, Miyatake's HSV vector is recombinant with *lacZ* gene within the RR locus. While RR (ICP6) gene is specific for proliferating and nonproliferating cells (dividing cell-specific) as noted by Miyatake because the RR enzyme is critical in the de novo synthesis of DNA precursors, the HSV vector designed by Miyatake is not tissue specific, e.g., vascular smooth muscle cells, unless the vector is directly injected into the area where the target cells are. A skilled artisan would have to perform a substantial amount of experimentation to properly and successfully combine the teachings of Martuza, Yamamura, Wagstaff, Foster and Miyatake in order to arrive at the claimed invention. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged; however, they are not found persuasive because the rejection is not based on using the vector of Miyatake et al., but rather on using a vector which comprises the calponin promoter (i.e., specific for proliferating smooth muscle cells (see the rejection above). Miyatake et al. was cited because they teach that vectors such as the one taught by Martuza et al., Yamamura et al., Wagstaff et al. and Foster et al. can be used to target proliferating smooth muscle cells. For these reasons, the rejection is maintained.

7. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633